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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/704,272	11/01/2000	Alan D. Attie	960296.96668	1921

7590 07/29/2004  
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EXAMINER

WEGERT, SANDRA L

ART UNIT PAPER NUMBER

1647

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/704,272	<b>Applicant(s)</b> ATTIE ET AL.	
	<b>Examiner</b> Sandra Wegert	<b>Art Unit</b> 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 13 May 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 4,7-10 and 12-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,6,11 and 22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 November 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

#### ***Status of Application, Amendments, and/or Claims***

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

Claims 4, 7-10 and 12-21 were withdrawn by the examiner in a previous Office Action (11 February 2003).

Claims 1-3, 5, 6, 11 are under examination in the Instant Application.

### **Claim Objections/Rejections**

#### ***35 USC § 112, first paragraph - lack of enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

**The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-3, 5, 6 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for the limitations of the claims wherein cholesterol uptake in the gut is inhibited by administering an ABC1 transporter inhibitor.

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Claims 1-3, 5, 6 and 11 read on a method of inhibiting cholesterol transport across the lumen of the gut of a human or animal, by administering an inhibitor of ABC1. Dependent claims recite sulfonylurea compounds as ABC inhibitors and agents given orally.

The specification discloses the *WHAM* mutation in chickens, in which a single nucleotide substitution results in an amino acid change at residue 89 of an ABC transporter. The specification documents the phenotypes of *WHAM* chickens as to pigmentation, phospholipid disposition and cholesterol transport (Specification pp. 25-27). *WHAM* chickens appear to share similarities to humans with Tangier's disease, namely: retention of cholesterol esters in skin and connective tissues (Lawn, et al, 1999, J. Clinical Investigation, 104: R25). Similarly, mutations in other human ABC transporters (e.g., ABCG5 and ABCG8) result in the hyperaccumulation of dietary plant sterols and cholesterol (Berge, et al, 2000, Science, 290: 1771) in homozygous individuals.

The instant Specification describes experiments in which the sulfonylurea *Glyburide* was used to inhibit cholesterol transport in vitro in normal mouse macrophages. However, the claims read on a method of inhibiting cholesterol uptake in the gut of an individual or animal and there is no enabling discussion or working examples disclosed in the instant application as to how to practice the method of inhibiting cholesterol uptake from the lumen of the gut *in-vivo*. Since regulation of cholesterol transport from the diet is complex, and involves more receptors than ABC receptors, and more ABC receptors than ABC1 (Berge, et al, 2000, Science, 290: 1771; Lawn, et al, 1999, J. Clinical Investigation, 104: R25) and possibly different mechanisms of cholesterol transport control in normal individuals, the effects of administering an ABC1 antagonist to inhibit cholesterol transport *in-vivo* are unpredictable.

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Furthermore, WHAM chickens and humans with Tangier's disease have reduced abilities for "reverse" cholesterol transport, meaning that the pathways leading to excretion of excess cholesterol are severely compromised. In addition, concentrations of high-density cholesterol carrier proteins ("HDL" in humans) in homozygous recessive individuals are at 1-5% of the normal or wild-type levels. These defects in cholesterol processing result in severe neuropathies, premature atherosclerosis, and early death (Remaley, et al, 1999, Proc. Natl. Acad. Sci., 96(22): 12685-12690; Asztalos, et al, 2001, Atherosclerosis, 156: 217-225). Since Tangier's disease is caused by a defective ABC transporter, one could reasonably expect that administration of an antagonist of the ABC transporter would mimic Tangier's disease, at least during the duration of drug administration.

However, applicants contend (page 4, 13 May 2004):

"Note that the applicants' invention is not to inhibit the action of ABC1 in the body generally. This invention is not intended to create individuals with Tangier disease or who have conditions similar to the WHAM chickens. The concept in this invention is to inhibit ABC1 activity principally in the intestinal cells. Thus the invention specifically recites that the inhibition of ABC1 activity is done only in the intestine, and it is for that reason that the drug is delivered orally and not intravenously. The Examiner is correct that if ABC1 inhibitor was delivered intravenously that it might have some of the effects that the Examiner speculates would occur, notably the inhibition of cholesterol secretion from the liver."

Applicants further remark (page 5, 13 May 2004):

"Note that several mechanisms are provided for inhibiting ABC1 activity selectively in the intestinal tract. There are genetic means and chemical means contemplated and enabled by the specification. It is further described that the ABC1 inhibitors could be antibodies, described in the specification on page 8. All of these agents are intended to be selectively applicable to the ABC1 activity in the intestine and not to circulate generally in the blood stream. That is the reason that oral activity is specifically recited in Claim 3, and the selective application of the inhibitor to the intestinal cells is recited in the other claims."

Applicant's comments have been fully considered but are not deemed persuasive for the following reasons:

The claims read on a method of inhibiting cholesterol uptake in the gut of an individual or animal. However, there is no enabling discussion or working examples disclosed in the instant application as to how to practice the method of *selectively* inhibiting cholesterol uptake in the gut of an animal or human, while avoiding inhibition of cholesterol secretion. The net effect of inhibiting the ABC1 transporter would not be to inhibit cholesterol uptake (e.g., from the diet), but rather to inhibit overall net cholesterol *excretion*. Humans with Tangier's disease have high concentrations of cholesterol in sensitive tissues, including blood vessels. Application of ABC1 inhibitors, such as sulfonylurea drugs, would result in a condition similar to Tangier's disease: a net decrease in cholesterol excretion and pathological levels of cholesterol esters in sensitive tissues such as nerves, glands and blood vessels. Orally-delivered ABC1 antibodies, besides not being confirmed as functional antagonists of the transporter, would most likely be digested, probably before they had ever reached their target. And orally-delivered sulfonylureas, such as the one used in the Specification, are distributed preferentially into the blood compartment within 30 minutes after ingestion (Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1993, McGraw-Hill, pages 1484-1488, esp. page 1485). It is difficult to contemplate an orally-delivered drug, or any other enabled means, for selectively inhibiting ABC transporters involved in cholesterol uptake, while preserving the function of those involved in cholesterol secretion.

Due to the large quantity of experimentation required to: determine how to administer, control side effects, and use an ABC inhibitor to inhibit net cholesterol uptake across the gut, the

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lack of direction or guidance in the specification regarding the same, the lack of working examples that use a sulfonylurea *in-vivo*, the state of the art showing the complexities of cholesterol transport regulation, and the breadth of the claims which embrace *in-vivo* inhibition of net cholesterol import --undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

### ***Conclusion***

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

### **Advisory information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time).

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If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW

22 July 2004



ELIZABETH KEMMERER  
PRIMARY EXAMINER